FEB 8 2013

510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K121942

1. Name of device

Adenovirus R-gene® US Assay, including the following components:

2. Reagents

Reagent	Description	Quantity / tube	Number of tubes	Number of reactions
R*10	Adenovirus and IC2 Amplification premix	450 µL	3	90
IC2	Internal Control 2	1 mL	1	100
W0	Water for extraction (Molecular grade)	1.8 mL	2	18
PC10	Adenovirus Positive amplification control	300 µL	1	30

3. Instrumentation and Software

The Adenovirus R-gene® US kit has to be used in combinations with 2 instruments:

- NucliSENS easyMag (bioMérieux) for the nucleic acid extraction
- SmartCycler® 2.0 Software Dx version 1.7b or 3.0 (Cepheid) for amplification

bioMérieux SA does not provide software. Software is provided by instrument manufacturers.

4. Classification

Device Class:	Class 2
Regulation:	21 CFR 866.3980; Respiratory viral panel multiplex nucleic acid assay
Product Code:	OCC

5. Premarket Notification submitter:

Name of Manufacturer:	bioMérieux SA
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6. Device to which equivalence is claimed and device to which comparison is claimed

Device to which equivalence is claimed

The assay reagent system which is the subject of this submission is claimed equivalent to the Gen-Probe Prodesse Incorporated test, which received 510(k) clearance from FDA as the Prodesse® ProAdeno™+ Assay, #K102952, cleared on 03-December-2010.

Device to which comparison is claimed

The comparison is performed against culture on shell vials followed by identification with D^3Ultra™ DFA Respiratory virus screening & ID kit, #k061101, cleared on 20-Nov-2006, claiming in their 510k the detection of the respiratory adenoviruses by DFA or after culture. Real-time PCR is a technology known to be very sensitive compared with DFA and more in relationship with the performances reached with the culture which allows an amplification of the viruses as the PCR amplifies the genome of the viruses. Viral culture is the reference method. For all these reasons, we have chosen the culture revealed with D^3 Ultra DFA Respiratory virus screening & ID kit for the comparison.

7. Intended Use of the Device

Adenovirus R-gene® US Assay is a Real Time PCR *in vitro* diagnostic test for the rapid and qualitative detection of Adenovirus viral DNA isolated and purified from nasopharyngeal swab or nasopharyngeal wash/aspirate specimens obtained from individuals exhibiting signs and symptoms of acute respiratory infection. The intended use for this test is to aid in the diagnosis of respiratory Adenovirus infection in humans in conjunction with other clinical and laboratory findings. The test detects, but does not differentiate, Adenovirus species (A, B, C, D, E, F and G). Negative results do not preclude Adenovirus infection and should not be used as the sole basis for treatment or other patient management decisions.

8. Description of the Device

The ADENOVIRUS R-gene® US Assay is a Taqman based Real Time PCR Assay that enables detection of human Adenovirus DNA and Internal Control 2.
An overview of the procedure is as follows:

1. Collect nasopharyngeal specimens from symptomatic patients. Two transport media may be used UTM or M4RT (not provided with kit).
2. Add an Internal Control 2 (IC2) to every sample and to the W0 reagent, to monitor for inhibitors present in the specimens and check the extraction step.
3. Perform extraction and purification of nucleic acids using a NucliSENS® easyMAG™ System (bioMérieux) and the Automated Magnetic Extraction Reagents (bioMérieux).
4. Add purified nucleic acids to the ready to use R^x10 amplification premix included in the ADENOVIRUS R-gene® US kit. The R^x10 amplification premix contains oligonucleotide primers and target-specific oligonucleotide probes. The primers and probes are complementary to a fragment located in the Hexon gene region and to the internal control 2 DNA sequence. The probes are dual-labeled with a reporter dye attached to the 5'-end and a quencher dye attached to the 3'-end (see table below).

Analyte	Gene targeted	Probe Fluorophore	Absorbance Peak	Emission Peak	Instrument Channel
Adenovirus	Hexon	FAM	495 nm	530 nm	FAM
Internal Control 2	N/A	HEX	535 nm	560 nm	Cy3

5. Perform amplification of DNA in a Cepheid SmartCycler® 2.0 instrument. In this process, the probe anneals specifically to the DNA template followed by primer extension and amplification. The 5' – 3' exonuclease activity of the Taq polymerase cleaves the probe separating the reporter dye from the quencher. This generates an increase in fluorescent signal upon excitation from a light source. With each cycle, additional reporter dye molecules are cleaved from their respective probes, further increasing fluorescent signal. The amount of fluorescence at any given cycle is dependent on the amount of amplification products present at that time. Fluorescent intensity is monitored during each PCR cycle by the real-time instrument.
6. Interpretation.

8.1. Components of Adenovirus R-gene® US

Reagents	Description	Composition	Quantity / tube	Nb of reactions	Concentration	Source	Form
R^x10	Adenovirus and IC2 Amplification premix	Specific Adenovirus and IC2 primers and probes, Tris buffer, $MgCl_2$, dNTPs, Taq polymerase, Rox Carboxy x Rhodamine, Amonium sulfide, BSA, H2O	450 µL	90 (3 tubes provided)	Ready to use	bioMérieux SA	Liquid
IC2	Internal Control 2	Native Phix bacteriophage, Phast Media medium Glycerol	1 mL	100	Ready to use	bioMérieux SA	Liquid
W0	Water for extraction (Molecular grade)	Water	1.8 mL	18 (2 tubes provided)	Ready to use	bioMérieux SA	Liquid
PC10	Adenovirus Positive control	Composite plasmid, Tris buffer, yeast tRNA	300 µL	30	Ready to use	bioMérieux SA	Liquid

8.2. Required Components Not Sold by bioMérieux SA

Plastic ware and Consumables:

- Polyester, rayon or nylon tipped nasopharyngeal swabs
- Sterile suction catheter (#8) for nasopharyngeal washes/aspirates specimen
- 1.5 mL polypropylene microcentrifuge tubes
- Sterile filter or positive displacement micropipettor tips
- EasyMAG™ System Disposables (Sample Vessels and Tips)
- Biohit Pipette Tips for use with easyMAG™ System
- Greiner Break Four uncoated plates for use with easyMAG™ System
- Cepheid PCR reaction tubes, 25 µL
- Single use latex or similar gloves

Reagents:

- bioMérieux NucliSENS® easyMAG™ reagents (Buffer 1 Cat.#280130, Buffer 2 Cat.#280131, Buffer 3 Cat.#280132, Magnetic Silica Cat. #280133, Lysis Buffer (bottles) Cat.# 280134
- Transport medium:
  - Universal Transport Medium from DHI
  - MicroTest™ M4RT Transport from Remel
- Proteinase K Solution, 600 mAU/mL (Novagen – Merck – 71049-3/71049-4)
- Molecular grade water
- Sterile physiologic buffer

Equipment:

- -18°C/-22°C Freezer
- bioMérieux NucliSENS® easyMAG™ System with Software version 2.0.
- Cepheid SmartCycler 2.0 Instrument with Dx Software version 1.7b or 3.0
- Micropipettors (range between 1-10 µL, 10-200µL and 100-1000µL)
- Mini-centrifuge with adapter for Cepheid Reaction Tubes.
- Cepheid cooling block
- U.V light
- Workstation or Plexiglas screen for samples and premix distribution

8.3. Assay Instruments and Software

Instruments

The ADENOVIRUS R-gene® US kit has to be used in combinations with 2 instruments:

- NucliSENS easyMag (bioMérieux) for the nucleic acid extraction
- SmartCycler® 2.0 Software Dx version 1.7b or 3.0 (Cepheid) for amplification.

Modes of operation:

The bioMérieux NucliSens easyMAG is an automated nucleic acid isolation and purification system that is based upon the silica extraction technology. The NucliSENS easyMAG is capable of processing a total of 24 reactions with variable sample types, sample volumes, and elution volumes within a single run. Nucleic acid is purified within a single cartridge by several steps that include lysis and binding of nucleic acid to high affinity magnetic silica beads, a series of wash steps and heated elution of purified nucleic acid from the silica beads.

The Cepheid SmartCycler® 2.0 Real Time instrument with Dx software version 1.7b or 3.0a is used to perform real time PCR amplification and detection of nucleic acid. The Cepheid SmartCycler® instrument is an integrated nucleic acid amplification and detection instrument system based on Cepheid's proprietary microprocessor-controlled I-CORE module. For purified DNA samples, the SmartCycler® instrument enables polymerase chain reaction (PCR) for the amplification of DNA, and hybridization of fluorogenic target- specific probes for the detection of the amplified DNA.

Software

bioMérieux SA does not provide software. Software is provided by instrument manufacturer.

9. SUBSTANTIAL EQUIVALENCE INFORMATION

9.1. Predicate device name:

Gen-Probe Prodesse Incorporated - Prodesse® ProAdeno™+ Assay

9.2. Predicate device 510(k) number

K102952

9.3. Comparison with predicate

The Adenovirus R-gene® US test is claimed substantially equivalent to the Gen-Probe Prodesse Incorporated - Prodesse® ProAdeno™+ Assay (K102952).

Similarities and differences between the tests are outlined below:

Item	Predicate device	bioMérieux SA device
Name	**Prodesse® ProAdeno™+ Assay**	**ADENOVIRUS R-gene® US** Reference: 69-010B-US
Manufacturer	Gen-Probe Prodesse Incorporated	bioMérieux SA
510k number	K102952	K121942
Regulation section Classification name Product code Device class Panel	866.3980 Respiratory viral panel multiplex nucleic acid assay OCC Class II Microbiology (83)	866.3980 Respiratory viral panel multiplex nucleic acid assay OCC Class II Microbiology (83)
Intended use / Virus detection	Qualitative detection of human Adenovirus viral nucleic acids.	Same
Technology / Detection	Real Time PCR Detection: Instrument based Fluorogenic target-specific hybridization	Same
Samples type	NP swabs	NP swabs and NP washes/aspirates
Collection and transport medium	M4 and M5 Viral Transport Medium (Remel), UVT (Becton Dickinson), UTM (Copan)	- Universal Transport Medium from DHI (21CFR866.2390) - MicroTest™ M4RT Transport from Remel (21CFR866.2390)
Sample extraction procedure Nucleic Acid Isolation	MagNA Pure LC System (Roche), NucliSENS easyMAG (bioMérieux)	NucliSENS easyMag (bioMérieux) Magnetic silica based method (R. BOOM technology)
Nucleic acid amplification and fluorescence / Instrument / Assay platform	Cepheid SmartCycler® II System	SmartCycler® 2.0 Software Dx version 1.7b or 3.0 (Cepheid)
Assay controls included in kit	Adenovirus positive DNA transcript control and an Internal DNA/RNA control provided	- Positive control - Negative control - Extraction / Inhibition control
Results	Negative Positive Unresolved	Same

10. Standard/Guidance Document Referenced (if applicable):

Not applicable

11. Test Principle:

11.1. Samples collection

11.1.1. Nasopharyngeal wash/aspirate

Nasopharyngeal Washes/aspirates can be collected using a sterile suction catheter (#8) connected to the specimen trap while the patient is in a supine position.
Nasopharyngeal Washes/aspirates can be collected by instilling and aspirating 1 to 5 mL of sterile physiological fluid into a nostril.
Nasopharyngeal Washes/aspirates can be diluted two fold in viral transport medium, Universal Transport Medium (UTM) from DHI or MicroTest M4RT from Remel (see chapter "Materials required but not provided").

11.1.2. Nasopharyngeal swab

Deeply insert the swab into a nostril in the direction parallel to the palate.
Leave the swab in place for 10 seconds to allow the collection of sample. Rotate the swab 2 or 3 times so it rubs against the nasal wall.
Remove the swab and place it in a sterile tube containing 3mL of viral transport medium, Universal Transport Medium (UTM) from DHI or MicroTest M4RT from Remel (see chapter "Materials required but not provided").
Break off the swab, cap the tube appropriately and send to the laboratory.

11.2. Sample transport

Samples are withdrawn and transferred under the laboratory instructions. For samples to be transported, each laboratory has to check their local legislation for hazardous and infectious material transport.

11.3. Sample storage

The ADENOVIRUS R-gene® US Assay IFU recommends that samples be stored refrigerated +2°C/+8°C for up to 24 hours prior to processing or stored at -18°C/-22°C for 4 days or -78°C/-82°C for longer period.

11.4. Nucleic acid extraction

The bioMérieux NucliSens easyMAG is an automated nucleic acid isolation and purification system that is based upon the silica extraction technology. The easyMAG is capable of processing a total of 24 reactions with variable sample types, sample volumes, and elution volumes within a single run. Nucleic acid is purified within a single cartridge by several steps that include lysis and binding of nucleic acid to high affinity magnetic silica beads, a series of wash steps and heated elution of purified nucleic acid from the silica beads.

11.5. Nucleic acid amplification and detection

The Cepheid SmartCycler® 2.0 Real Time instrument with Dx software version 1.7b or 3.0a is used to perform real time PCR amplification and detection of nucleic acid. The Cepheid SmartCycler® instrument is an integrated nucleic acid amplification and detection instrument system based on Cepheid's proprietary microprocessor-controlled I-CORE module. For purified DNA samples, the SmartCycler® instrument enables polymerase chain reaction (PCR) for the amplification of DNA, and hybridization of fluorogenic target- specific probes for the detection of the amplified DNA.

11.6. Adenovirus assay

The real-time PCR process simultaneously amplifies and detects nucleic acid targets in a single closed-tube reaction. The ADENOVIRUS R-gene® US Assay enables simultaneous detection of AdV and Internal Control 2 DNA. The whole process is based on two steps: nucleic acid isolation and Real Time PCR amplification/detection. Human respiratory specimens (nasopharyngeal swabs, nasopharyngeal washes/aspirates) from symptomatic patients are processed initially to isolate and purify viral nucleic acid from the cellular specimen matrix. Each purified nucleic acid sample is added to the R^{x}10 amplification premix (Ready to use, Taq polymerase included). The R^{x}10 amplification premix contains oligonucleotide primers complementary to a fragment of the Hexon gene region coding for the hexagonal capsomers for AdV and target-specific oligonucleotide probes dual-labelled with a reporter dye and a quencher dye. Amplification proceeds during which, the probe anneals specifically to a region of the template between the forward and reverse primers. As primer extension and amplification occurs, the exonuclease activity of the Taq polymerase cleaves the probe separating the reporter dye away from the quencher. This generates an increase in fluorescent signal upon excitation from a LED light source of appropriate wavelength. With each cycle, additional reporter dye molecules are cleaved from their respective probes, yielding increased fluorescence signal. The amount of fluorescence at any given cycle is dependent on the amount of PCR product (amplicons) present at that time. Fluorescent intensity is monitored at each PCR cycle by fluorescent detection modules within the real-time instrument.

11.7. Explanation of the assay

The ADENOVIRUS R-gene® US Assay is a Taqman based Real Time PCR Assay that enables detection of human Adenovirus DNA and Internal Control 2.
An overview of the procedure is as follows:

1. Collect nasopharyngeal specimens from symptomatic patients. Two transport media may be used UTM or M4RT (not provided with kit).
2. Add an Internal Control 2 (IC2) to every sample and to the W0 reagent, to monitor for inhibitors present in the specimens and check the extraction step.
3. Perform extraction and purification of nucleic acids using a NucliSENS® easyMAG™ System (bioMérieux) and the Automated Magnetic Extraction Reagents (bioMérieux).
4. Add purified nucleic acids to the ready to use R^{x}10 amplification premix included in the ADENOVIRUS R-gene® US kit. The R^{x}10 amplification premix contains oligonucleotide primers and target-specific oligonucleotide probes. The primers and probes are complementary to a fragment located in the Hexon gene region and to the internal control 2 DNA sequence. The probes are dual-labeled with a reporter dye attached to the 5'-end and a quencher dye attached to the 3'-end (see table below).

Analyte	Gene targeted	Probe Fluorophore	Absorbance Peak	Emission Peak	Instrument Channel
Adenovirus	Hexon	FAM	495 nm	530 nm	FAM
Internal Control 2	N/A	HEX	535 nm	560 nm	Cy3

5. Perform amplification of DNA in a Cepheid SmartCycler® 2.0 instrument. In this process, the probe anneals specifically to the DNA template followed by primer extension and amplification. The 5' – 3' exonuclease activity of the Taq polymerase cleaves the probe separating the reporter dye from the quencher. This generates an increase in fluorescent signal upon excitation from a light source. With each cycle, additional reporter dye molecules are cleaved from their respective probes, further increasing fluorescent signal. The amount of fluorescence at any given cycle is dependent on the amount of amplification products present at that time. Fluorescent intensity is monitored during each PCR cycle by the real-time instrument.
6. Interpretation.

12. Performance Characteristics

12.1. Limit of Detection (LoD) and Analytical Reactivity

The objective of the Analytical Sensitivity study was to determine the Limit of Detection (LoD) of Adenovirus R-gene® US real time PCR assay.
Prior to the LoD determination, a homology study allowed to classify the 60 Human Adenovirus known, into 21 different groups, according to the number and the position of mismatches of the best primer (forward and reverse) and the best probe which comprise the Adenovirus R-gene® 69-010B-US amplification/detection premix.
One Human Adenovirus (AdV) type was chosen for each group of homologies, for each of the 21 different sequences.
The LoD were determined, on 4 to 6 dilutions, for a total for 60 to 90 amplifications/detections, for the 21 selected Human Adenoviruses, plus Adenovirus serotype 2, to complete the specie C, for a total of 22 LoD determinations.
The table below summarizes the LoD values at 95% for the 22 viral types, after limiting dilution analysis.

Homologies Groups	HAdV Species	HAdV Types	LoD 95% TCID50/mL
# 1	A	HAdV 12	0.000416
# 2		HAdV 18	18
# 3		HAdV 31	10
# 4	B1	HAdV 3	0.00316
# 5		HAdV 7	0.0445
# 6	B2	HAdV 11	889
# 7	C	HAdV 1	0.0209
# 8-1		HAdV 2	0.00625
# 8-2		HAdV 5	0.044
# 9		HAdV 6	0.00512
# 10	D	HAdV 39	0.0158
# 11		HAdV 15	0.316
# 12		HAdV 9	0.1
# 13		HAdV 8	0.000812
# 14		HAdV 17	158
# 15		HAdV 25	0.05
# 16		HAdV 28	28.1
# 17		HAdV 42	0.05
# 18	E	HAdV 4	0.183
# 19	F	HAdV 40	0.0104
# 20		HAdV 41	0.158
		Max	889
		Min	0.000416

Homologies Groups	HAdV Species	HAdV Types	LoD 95% copies/mL
# 21	G	HAdV 52*	5000 copies/mL*

* *Adenovirus type 52 was not available for culture and thus a plasmid was constructed and the LoD was determined to be 5000 copies/mL by qPCR.*

The limits of detection at 95% are ranged between 889 and 0.000416 $TCID_{50}$/mL.
The homologies studies and the Limit of Detection results demonstrate the capability of Adenovirus R-gene® US real time assay to detect the Adenovirus types 1 to 60.

12.2. Analytical Specificity

A panel of 61 potentially cross reacting microorganisms consisting of 34 viral and 27 bacterial, representing common respiratory pathogens or flora commonly present in the nasopharynx was evaluated for cross reactivity.
Each potential cross reactant was individually spiked at a high level into a negative NP wash/aspirate matrix.
The Adenovirus R-gene® US assay did not cross-react with any of the Analytical Specificity Panel samples tested.

12.3. Carry-Over / Cross-Contamination

This study assessed the level of the carry-over/cross-contamination with the Adenovirus R-gene® US Assay by testing simulated human adenovirus (HAdV) High Positive samples run in series with HAdV Negative samples. The High Positive samples consisted of negative nasopharyngeal washes/aspirates spiked with a level 4 logs above the Limit of Detection (LoD) of a titered strain of HAdV-4. The samples were processed and extracted in a High Positive/Negative alternating fashion on the bioMérieux NucliSENS EasyMag extraction system and likewise processed and run on the Cepheid SmartCycler 2.0 instrument in an alternating fashion.
Eleven High Positive and eleven Negative samples and a Negative Control were extracted per run on the easyMAG for a total of 55 High Positive samples and 55 Negative samples over 5 extraction runs and 4 amplification runs.
When tested with high positive samples, no carry-over contamination was seen for the Adenovirus R-gene® 69-010B-US assay.
The workflow and design of the assay have been shown to be robust against carry-over contamination and therefore the requirement (less than or equal to 2%) has been met.

12.4. Freeze / Thaw studies

Freeze / thaw studies were carried out to demonstrate that the Adenovirus R-gene® US reagents provided can undergo up to ten freeze and thaw cycles for the Adenovirus R-gene® R^x10 ready-to-use amplification/detection premix and the Internal Control 2, and up to twenty-nine freeze and thaw cycles for the Positive Control 10.

12.5. Microbial Interference

To determine the potential interference of common nasal micro-organisms on qualitative Adenovirus detection, a panel of micro-organisms was spiked into Adenovirus positive nasopharyngeal washes/aspirates containing Adenovirus at two times the limit of detection (2 x LoD).
These samples were extracted and tested with the Adenovirus R-gene® 69-010B-US real time PCR assay. Adenovirus detection and Ct values were compared back to a reference sample with no additional micro-organism.
The Adenovirus R-gene® US real time PCR assay did not cross-react with any of the micro-organisms tested to give a significant change in the Adenovirus Ct data. Adenovirus was detected regardless of whether an additional micro-organism was present, indicating that there was no interference caused by other micro-organisms.

12.6. Chemical Interference

To determine the potential interference of endogenous and exogenous chemical PCR inhibitors on Adenovirus detection, clinically relevant amounts of interfering substances were added to nasopharyngeal samples spiked with Adenovirus at 1.3 x LoD and 6.6 x LoD. A reference sample with no interfering substance was included at both 1.3 and 6.6 x LoD.
The Adenovirus R-gene® US real time PCR assay performance does not appear to be afftected by any of the endogenous or exogenous interfering substances at the concentrations tested. Both concentrations of Adenovirus were detected regardless of the potential interfering substance present, with no clinically significant change in the Ct values.

12.7. Assay Cut-off

The « cut-off value » represents the fluorescent intensity signal (reported in Arbitrary Fluorescent Units, AFU) at which a "positive" reaction reaches a relative fluorescent intensity above the background or baseline of a "negative" reaction. If a sample exceeds the threshold in a detection channel during PCR, the sample is considered positive for that channel. If the sample does not exceed the threshold for a detection channel by the last PCR cycle, the sample is considered negative for that channel.
Cut-off determination for Adenovirus detection at 530nm was performed through testing of series of negative samples and high negative samples, for a total of 218 samples.
The threshold default value (30 AFU) of the SmartCycler 2.0 was confirmed to be the correct cut-off value for Adenovirus R-gene® US assay, and was further confirmed in a preliminary study, performed at Caen Hospital (France), on 184 clinical samples, prior to US clinical studies. Analysis of the U.S. clinical studies results, on 1,576 clinical samples, confirmed the 30 AFU value as the better cut-off to achieve the best sensitivity and specificity.

SmartCycler 2.0 default cut-off value of 30 AFU, for Internal Control 2 detection at 560nm, was challenged by analyzing the results obtained for amplification tubes with Internal Control 2 in water (« IC2W0 ») and amplifications tubes with no target (« No target »).
Initial validation was performed on 28 runs, before the preliminary study at Caen Hospital, followed by 65 new runs, and US clinical studies runs.
The threshold default value (30 AFU) of the SmartCycler 2.0, for Internal Control 2 (560nm channel), was validated to be the correct cut-off value for Adenovirus R-gene® US assay.

12.8. Precision / Reproducibility

The precision of the ADENOVIRUS R-gene® US assay was evaluated using artificial samples consisting of human nasopharyngeal matrix spiked with Adenovirus strains at 3 different inputs. The precision study was determined with respect to the complete assay procedure, comprising all steps from the nucleic acid extraction of the sample to the final result.

The panel of tested samples was comprised of three different viral inputs, tested in 3 replicates per run: "High Negative" samples corresponding to approximately 0.01 x LOD, "Low Positive" samples corresponding to approximately 2.0 x LOD and "Moderate Positive" samples corresponding to approximately 10.0 x LOD.

The precision was analyzed by determining for each viral load the percentage of correct ADENOVIRUS R-gene® US test results based on the expected outcome.

A "within-laboratory" precision study was performed at bioMérieux SA – ARGENE site over 5 days, with 2 operators, using 1 instrument and 1 lot of reagent.
The overall percent agreement with the expected outcome was 100% for the moderate positive input (10.0xLoD), 95% for the low positive input (2.0xLoD) and 100% for the high negative input (0.01xLoD) as described in the table below. The table also indicate the Mean of the Ct values for the three types of samples, the standard deviations, and coefficients of variation.

Within-Laboratory Variation

			Ct value		
Sample Input	**% Agreement**	**95% CI**	**Mean**	**SD**	**%CV**
Moderate Positive (MP)	100 % (150/150)	97.6 - 100 %	28.73	0.47	1.6 %
Low Positive (LP)	95 % (114/120)	89.4 - 98.1 %	32.90	3.00	9.1 %
High Negative (HN)	100 % (90/90)	96 - 100 %	24.19*	0.17	0.7 %
Total Agreement	98.3 % (354/360)	96.4 - 99.39 %			

** Mean Ct calculated from IC2 control*

A "between-laboratory" precision study was performed at 3 sites (external sites in the US), over 5 days, with 2 operators at each site, 1 instrument at each site and 1 lot of reagents.
The overall percent agreement with the expected outcome was 100% for the moderate positive input (10xLoD), 98.6% for the low positive input (2xLoD) and 98.5% for the high negative input (0.01xLoD) as described in the table below. The table also indicates the Mean of the Ct values for the three types of samples, the standard deviations, and coefficients of variation.

Between-Laboratory Variation

Sample Input	Site 1	Site 2	Site 3	Total Agreement	Ct Value		
					Mean	SD	%CV
	% Agreement	% Agreement	% Agreement	% Agreement and 95% CI			
High Negative (HN)	100% (90/90)	95.6% (86/90)	100% (90/90)	98.5% (266/270) 96.3-99.6%	24.12*	0.36	1.5%
Low Positive (LP)	99.2% (119/120)	99.2% (119/120)	97.5% (117/120)	98.6% (355/360) 96.8-99.6%	32.0	2.17	6.8%
Moderate Positive (MP)	100% (150/150)	100% (150/150)	100% (150/150)	100% (450/450) 99.2-100%	28.78	1.35	4.7%
Total Agreement	99.7% (359/360)	98.6% (355/360)	99.2% (357/360)	99.2% (1071/1080) 98.4-99.6%			

** Mean CT calculated from IC2 control*

The overall percent agreement for the ADENOVIRUS R-gene™ US assay was 99.13%

			Site 1			Site 2			Site 3					
ID Panel	Species	Concentration	Agreement with expected result	AdV Average Ct Value (FAM)	% CV	Agreement with expected result	AdV Average Ct Value (FAM)	% CV	Agreement with expected result	AdV Average Ct Value (FAM)	% CV	Total Agreement with expected result	Overall Average CT Value	Overall % CV
Panel 1	AdV 2	2 x LoD	30/30 (100%)	33.65	3.02	29/30 (96,6%)	33.43	2.50	28/30 (93,3%)	34.13	7.55	87/90 (96.6%)	33.92	5.14%
Panel 2	AdV 3	0,01 x LoD	30/30 (100%)	neg	na	27/30 (0,90%)	neg	na	30/30 (100%)	neg	na	87/90 (96.6%)	na	na
Panel 3	AdV 4	2 x LoD	29/30 (100%)	32.50	1.60	30/30 (100%)	32.15	1.98	29/30 (96,6%)	32.93	5.33	88/90 (97.7%)	32.52	3.53%
Panel 4	AdV 2	10 x LoD	30/30 (100%)	29.95	1.05	30/30 (100%)	29.95	1.03	30/30 (100%)	30.06	1.08	90/90 (100%)	29.98	1.06%
Panel 5	VRS +	Ct =25	30/30 (100%)	neg	na	30/30 (100%)	neg	na	30/30 (100%)	neg	na	90/90 (100%)	na	na
Panel 6	AdV 3	2 x LoD	30/30 (100%)	29.01	0.92	30/30 (100%)	29.00	1.05	30/30 (100%)	28.99	0.75	90/90 (100%)	29.00	0.91%
Panel 7	AdV 5	10 x LoD	30/30 (100%)	28.73	0.75	30/30 (100%)	28.37	3.22	30/30 (100%)	28.65	0.98	90/90 (100%)	28.58	2.03%
Panel 8	AdV 3	10 x LoD	30/30 (100%)	26.58	0.69	30/30 (100%)	26.69	1.61	30/30 (100%)	26.48	0.78	90/90 (100%)	26.58	1.14%
Panel 9	AdV 4	0,01 x LoD	30/30 (100%)	neg	na	30/30 (100%)	neg	na	30/30 (100%)	neg	na	90/90 (100%)	na	na
Panel10	PN Neg		30/30 (100%)	neg	na	30/30 (100%)	neg	na	30/30 (100%)	neg	na	90/90 (100%)	na	na
Panel 11	AdV 4	10 x LoD	30/30 (100%)	29.27	0.68	30/30 (100%)	29.46	6.02	30/30 (100%)	29.32	0.93	90/90 (100%)	29.35	3.52%
Panel 12	AdV 1	10 x LoD	30/30 (100%)	29.39	0.92	30/30 (100%)	29.01	3.19	30/30 (100%)	29.76	1.35	90/90 (100%)	29.39	2.29%
Panel 13	AdV 2	0,01 x LoD	30/30 (100%)	neg	na	29/30 (96,6%)	neg	na	30/30 (100%)	neg	na	89/90 (98.8%)	na	na
Panel 14	AdV 1	2 x LoD	30/30 (100%)	31.96	1.86	30/30 (100%)	32.49	2.61	28/30 (93.3%)	33.44	2.72	88/90 (97.7%)	32.63	3.06%
Total % Agreement			419/420 (99.76%)			415/420 (98.8%)			415/420 (98.8%)			1249/1260 (99.13%)		

12.1. Prevalence / expected values

The prevalence is closely related to the patient population and the method of detection. Collection, handling and transport may also influence the prevalence. The adenovirus prevalence with the molecular detection is often higher than with culture or antigen detection. The expected values with this kit observed during the clinical study are presented in the table below.

Swab prospective study

Subject Age	Number	Total Adeno R-gene US positive	Expected value	Total DHI positive	Observed Prevalence
< 2	519	45	8.7%	25	4.8%
2-5	280	26	9.3%	14	5.0%
6-19	229	11	4.8%	5	2.2%
19-64	112	5	4.5%	4	3.6%
>65	43	0	ND	0	ND
Total	1183	87	7.35%	48	4.06%

Nasopharyngeal Wash/Aspirate prospective study

Subject Age	Number	Total Adeno R-gene US positive	Expected value	Total DHI positive	Observed Prevalence
< 2	275	33	12.0%	17	6.2%
2-5	57	7	12.3%	2	3.5%
6-19	55	2	3.6%	2	3.6%
19-64	5	0	0.0%	0	0.0%
>65	1	0	ND	0	ND
Total	393	42	10.69%	21	5.34%

12.2. Clinical Performance

Clinical Study Design

Performance characteristics of the Adenovirus R-gene® US assay were determined in a multi-center prospective investigational study employing 3 geographically diverse institutions in the US from September 2010 – November 2011.

The Adenovirus R-gene® US assay was compared with rapid culture (shell vial) followed by direct fluorescent antibody (DFA) screening and identification, a FDA-cleared method, the D3Ultra™ DFA Respiratory Virus screening & ID kit from Diagnostic Hybrids (DHI).

Each U.S site analyzed around 280-650 samples (swabs and NP washes/aspirates), for a total of 1581 samples of which 5 were excluded due to none compliance with clinical protocol. Among 1576 samples analyzed, no invalid result was reported.

The studies were performed on the remnant of the specimen collected after the routine clinical care without demographic inclusion criteria. The nasopharyngeal sample volume is sufficient to perform the study. The inital test with the ADENOVIRUS R-gene® US can be performed up to 5 days after sample collection.

Overall Clinical Study Results: Agreement of ADENOVIRUS R-gene® US with rapid culture revealed by DHI test

Results from the ADENOVIRUS R-gene® US assay compared with results of viral culture followed by DFA staining with DHI test are presented below respectively for swab and nasopharyngeal wash/aspirate specimens:

- **Swab Specimens**

  A total of 1186 swab specimens were collected of which 1183 had reportable results and are included in the analysis. There were 3 specimens excluded due to non-compliance with the clinical protocol.

  There were 48 final evaluable specimens that were positive for Adenovirus after rapid culture. ADENOVIRUS R-gene® US had an estimated sensitivity of 91.7% (95% CI 80.0%-97.7%), and an estimated specificity of 96.2% (95% CI 94.9%-97.2%).

Adenovirus Comparison Results – Swab Specimens

		Reference Method			
		+	-	Total	Comments
Adenovirus R-gene ® 69-010 US	+	**44**	**43** [a]	87	sensitivity 91.7% (80.0%-97.7%) 95%CI
	-	**4** [b]	**1092**	1096	specificity 96.2% (94.9%-97.2%) 95%CI
		48	1135	1183	

a Among the 43 negative samples for rapid culture and positive for Adenovirus, 42 were confirmed as positive for adenovirus using Real Time PCR.

b Among the 4 positive samples for rapid culture and negative for Adenovirus, 1was confirmed as positive for adenovirus using Real Time PCR.

- **NP Wash/Aspirate Specimens**

A total of 395 NP wash/aspirate specimens were collected of which 393 had reportable results and are included in the analysis. There were 2 specimens excluded due to non-compliance with the clinical protocol.

There were 21 final evaluable specimens that were positive for Adenovirus after rapid culture. ADENOVIRUS R-gene® US had an estimated sensitivity of 100% (95% CI 86.7%-100%) and an estimated specificity of 94.4% (95% CI 91.5%-96.5).

Adenovirus Comparison Results – NP Wash/Aspirate specimens

		Reference Method			
		+	-	Total	Comments
Adenovirus R-gene ® 69-010 US	+	**21**	**21** [a]	42	sensitivity 100% (86.7%-100%) 95%CI
	-	**0**	**351**	351	specificity 94.4% (91.5%-96.5%) 95%CI
		21	372	393	

a Among the 21 negative samples for rapid culture and positive for Adenovirus, 19 were confirmed as positive for adenovirus using Real Time PCR.

13. Proposed labeling

The proposed labeling is complete.

14. Conclusion

The information in this premarket notification is complete and supports a substantial equivalence decision.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-002

FEB 8 2013

Argene SA of BioMérieux
C/O Eric Brisson
Parc Technologique Delta Sud
Varilhes, FR 09120

Re: k121942
Trade/Device Name: Adenovirus R-gene® US
Regulation Number: 21 CFR 866.3980
Regulation Name: Respiratory viral panel multiplex nucleic acid assay
Regulatory Class: Class II
Product Code: OCC
Dated: December 20, 2012
Received: December 28, 2012

Dear Mr. Brisson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostics and Radiological Health at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Sally A. Hojvat

Sally Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

Intended Use

510(k) Number (if known): k121942

Device Name: Adenovirus R-gene® US

Intended Use:

Adenovirus R-gene® US Assay is a Real Time PCR *in vitro* diagnostic test for the rapid and qualitative detection of Adenovirus viral DNA isolated and purified from nasopharyngeal swab or nasopharyngeal wash/aspirate specimens obtained from individuals exhibiting signs and symptoms of acute respiratory infection. The intended use for this test is to aid in the diagnosis of respiratory Adenovirus infection in humans in conjunction with other clinical and laboratory findings. The test detects, but does not differentiate, Adenovirus species (A, B, C, D, E, F and G). Negative results do not preclude Adenovirus infection and should not be used as the sole basis for treatment or other patient management decisions.

Prescription Use ___X___ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH; Office of In Vitro Diagnostics and Radiological Health (OIR)

Division Sign-Off

Office of In Vitro Diagnostics and Radiological Health

510(k) K121942